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A proposal to create an extension to the European baseline series

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Summary

Background. The current European baseline series consists of 30 allergens, and was last updated in 2015.

Objectives. To use data from the European Surveillance System on Contact Allergies (ESSCA) to propose an extension to the European baseline series in response to changes in environmental exposures.

Methods. Data from departmental and national extensions to the baseline series, together with some temporary additions from departments contributing to the ESSCA, were collated during 2013–2014.

Results. In total, 31689 patients were patch tested in 46 European departments. Many departments and national groups already consider the current European baseline series to be a suboptimal screen, and use their own extensions to it. The haptens tested are heterogeneous, although there are some consistent themes. Potential haptens to include in an extension to the European baseline series comprise sodium metabisulfite, formaldehyde-releasing preservatives, additional markers of fragrance allergy, propolis, Compositae mix, and 2-hydroxyethyl methacrylate.

Conclusion. In combination with other published work from the ESSCA, changes to the current European baseline series are proposed for discussion. As well as addition of the allergens listed above, it is suggested that primin and clioquinol should be deleted from the series, owing to reduced environmental exposure.

Key words: Compositae mix; European baseline series; formaldehyde releaser; fragrance; 2-hydroxyethyl methacrylate; propolis; sodium metabisulfite.

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Conflicts of interest. M. Wilkinson: attended a drug advisory board meeting for GlaxoSmithKline (alitretinoin). W. Uter: accepted travel reimbursement and honoraria for presentations given to cosmetic industry (associations) from them, and received a lecture fee from Almirall Hermal for educational lectures on contact allergy. The other authors do not declare a conflict of interest pertinent to this study.

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The allergens used in any baseline series constitute an empirical choice reflecting a variety of factors, not least the exposures of the local population. Considerations in choosing substances to test have been reviewed (1), and have guided subsequent revisions of the European baseline series (EBS), most recently in 2015 (2). In practice, revisions have been proposed and implemented by the European Environmental Contact Dermatitis Research Group (3) on behalf of the ESCD (www.escd.org).

The contents of a generally recommended baseline series such as the EBS should be based on a sufficiently broad and valid evidence base. Another function of a baseline series should be to include extensions for adaptation to changes in environmental exposures at a local, regional or national level. Those extensions that prove useful for most investigators will provide incontrovertible evidence to support their inclusion into a core baseline series. The aim of this article is to stimulate debate on the current allergens included in the EBS, with the aim of creating a more open and responsive process for updating the series, using data provided by the European Surveillance System on Contact Allergies (ESSCA) to generate initial discussion.

Method

The ESSCA network has already been described in previous publications (4). Briefly, clinical and demographic data, along with patch test results of the baseline series used in the departments, of all patients patch tested in the departments participating in the ESSCA are documented electronically in the local departments, by the use of diverse data capture software and partly the multilingual software WINALLDAT/ESSCA provided by the ESSCA (5). Anonymized data are pooled in the ESSCA data centre in Erlangen for further analysis (6) with R (version 3.3.2; www.R-project.org) software (7). Data from departmental and national extensions to the baseline series, together with some temporary additions, are also collated, provided that they have been tested in strictly consecutive patients to achieve comparability. These additional data may give an impression of the value of the respective allergens for future inclusion.

The study period was January 2013 to December 2014. The study included 12 European countries and, in total, 46 departments that contributed data on the EBS, with or without extensions and omissions. The present analysis is focused explicitly on allergens that were not part of the EBS that was valid at the time (8), but that have, however, been included in departmental and, preferably, national extensions to it, tested in consecutive patients. Hence, the present analysis is based on a subset of participating departments (see Acknowledgements), as some departments contributed only EBS data.

Altogether, 31 689 patients were registered who had been tested with the EBS (with or without additions), with readings at least between day (D) 3 and D5. TRUE Test® employing a hydrocellulose matrix for the haptens instead of pet. or water had been used in a relatively small number of patients (n = 1214), the vast majority of patients having been tested with pet.-based and water-based haptens, and investigator-loaded chamber systems. Moreover, two German departments use a 1-day patch test exposure, applied to 948 patients.

Results

In the years 2013 and 2014, 31 689 patients were patch tested in the 46 European departments. The characteristics of this clinical population and patch test results obtained with the EBS have been published previously (9). As the Danish and Slovenian and a few other single department(s) shared data on results obtained with the EBS 'as is', they did not contribute to the present analysis. The frequencies of doubtful reactions, irritant reactions and different grades of positive reaction are shown in Table 1a–k for those allergens that were tested in more than one department.

Moreover, the following allergens were tested in consecutive patients in single departments, and yielded the following results; this includes allergens that had been tested in different concentrations in other departments and are shown in Table 1:

- Imidazolidinyl urea 1% pet. [Italy-11]: 1217 patients tested; one + reaction (0.1% positive).
- Bronopol (2-bromo-2-nitropropane-1,3-diol) 0.3% pet. (UK-99): 2503 patients tested; 2 ?+ reactions and 16 + reactions (0.6% positive).

Results obtained with allergens that were not part of the EBS obtained with TRUE Test® are shown in Table 2. Note that TRUE Test® had been used in < 20 patients in Basel (Switzerland) and Amsterdam VU (The Netherlands); these results have been omitted, as selective testing cannot be excluded. Therefore, the results are restricted to the three Spanish departments and Groningen, The Netherlands.

Discussion

The results show that many departments and national groups already consider the current EBS to be a suboptimal screen, and use their own extensions to it. The haptens tested are, however, heterogeneous, although there are some consistent themes. In addition to being common,

Table 1. Pattern of reaction to allergens beyond the European baseline series valid during the study period tested in consecutive patients in more than one department of the European Surveillance System on Contact Allergies network. Allergens in pet., except where indicated otherwise

Department/country	n tested	% ?+/IR	% +	% ++/+++	% positive	% stand. positive	95%CI
(a) Sodium metabisulfite 1%							
UK	5969	0.2	1.4	1.5	2.9	2.9	2.4–3.3
NL-02	1969	1.3	4.6	0.4	5.0	4.9	3.9–5.8
PL-01	200	0	0.5	1.0	1.5	1.6	0–3.5
(b) Diazolidinyl urea 2%							
ES	1190	0	0.2	0.4	0.6	0.6	0.1–1.0
NL	2568	0.4	0.9	0	0.9	0.9	0.5–1.3
UK	6592	0.1	0.2	0.4	0.6	0.6	0.4–0.8
DE-01	282	2.1	0.7	0	0.7	1.0	0–2.5
IT-11	1217	0	0	0.1	0.1	0.1	0–0.2
LT-01	256	0	0	0	0	0	0–1.2
PL-01	203	0	0	0.5	0.5	0.6	0–1.7
(c) Imidazolidinyl urea 2%							
ES	1190	0	0.2	0.4	0.6	0.6	0.1–1.0
NL	2568	0.4	0.5	0.1	0.5	0.6	0.3–0.8
UK	5903	0.1	0.1	0.1	0.2	0.2	0.1–0.3
DE-01	283	0.7	0.4	0	0.4	0.7	0–2.2
FI-01	231	0.4	0	0.4	0.4	0.3	0–0.8
IT-02	576	0.2	0.7	0	0.7	0.6	0–1.3
LT-01	256	0	0	0	0	0	0–1.2
PL-01	203	0	0	0.5	0.5	0.6	0–1.7
(d) 2-Bromo-2–nitropropane-1,3-diol 0.25%							
UK	3401	0.1	0.8	0.2	0.9	0.9	0.6–1.3
IT-11	1217	0	0.1	0	0.1	0.1	0–0.2
LT-01	253	0	1.2	0.4	1.6	1.4	0–2.9
(e) 2-Bromo-2–nitropropane-1,3-diol 0.5%							
CH	1423	2.0	0.4	0.1	0.5	0.5	0.1–0.8
DE	1924	1.0	0.5	0.1	0.6	0.6	0.2–0.9
AT-25	292	0.3	0	0.3	0.3	0.3	0–0.8
ES-01	766	0	0.4	0.7	1.0	1.2	0.3–2.1
LT-01	3	0	0	0	0	0	0–63.2
NL-01	599	0	0	0	0	0	0–0.5
UK-08	1293	0.3	0.5	0.2	0.7	0.7	0.2–1.2
(f) Propolis 10%							
CH	2675	10.8	3.1	1.2	4.4	4.1	3.3–4.9
DE	3547	8.1	2.9	0.9	3.7	3.4	2.7–4.0
PL	1816	0.8	2.0	0.8	2.8	2.9	2.1–3.6
UK	2090	0.1	0.2	0	0.3	0.3	0.1–0.5
AT-25	509	1.6	5.9	0.4	6.3	5.6	3.6–7.7
IT-02	576	0.3	0.9	1.2	2.1	2.1	0.9–3.3
LT-01	256	0	0.4	0.4	0.8	0.7	0–1.9
(g) Oil of turpentine 10%							
CH	2672	1.4	0.7	0.4	1.1	1.0	0.6–1.3
DE	3555	1.8	1.1	0.3	1.3	1.1	0.8–1.5
AT-25	509	0.4	2.0	0.2	2.2	1.7	0.7–2.7
(h) Compositae mix 2.5%							
UK	3464	0	0.6	0.5	1.1	1	0.7–1.4
FI-01	232	0	0	0	0	0	0–1.3
(i) Compositae mix 5%							
CH	2698	1.1	0.7	0.5	1.2	1	0.7–1.4
DE	3590	1.5	1.0	1.1	2.1	2.0	1.5–2.5
AT-25	510	0.4	2.9	0.2	3.1	2.9	1.3–4.4
IT-01	4	0	0	0	0	0	0–52.7

Table 1. Continued

Department/country	n tested	% ?+/IR	% +	% ++/+++	% positive	% stand. positive	95%CI
(j) Compositae mix 6%							
IT	951	0.4	0.2	0.1	0.3	0.2	0–0.5
(k) Caine mix III 10%							
UK	7197	0.3	0.4	0.4	0.9	0.8	0.6–1.1
FI-01	231	2.2	0.4	0.4	0.9	1	0–2.4
PL-02	1613	0.5	2.1	0.4	2.5	2.7	1.9–3.6
(l) Carba mix 3%							
ES	1723	0.1	0.8	1.1	2.0	2.0	1.3–2.7
IT	1737	2.1	3.6	0.5	4.0	4.2	3.3–5.2
NL-02	1969	4.8	7.8	0.5	8.2	8.2	7.0–9.5
UK	7197	0.3	1.0	0	1.0	1.0	0.8–1.2

AT, Austria; CH, Switzerland; CI, confidence interval; DE, Germany; ES, Spain; FI, Finland; IR, irritant reaction; IT, Italy; LT, Lithuania; NL, The Netherlands; PL, Poland; UK, United Kingdom; Stand., standardized for age and sex.

Table 2. Patch test results obtained with the allergens from TRUE Test® that are not part of the European baseline series valid during the study period. The maximum reading between day (D) 3 and D5 (inclusive) was considered

Department/country	n tested	% ?+/IR	% +	% ++/+++	% positive	% stand. positive	95%CI
(a) Diazolidinyl urea							
ES	570	0	0.7	0	0.7	1.0	0–2.0
NL-01	599	0.3	0.3	0	0.3	0.3	0–0.8
(b) Imidazolidinyl urea							
ES	570	0.2	0.4	0	0.4	0.5	0–1.2
NL-01	599	0.8	0.2	0	0.2	0.2	0–0.5
(c) Quinoline mix							
ES	570	0	0.4	0	0.4	0.3	0–0.6
(d) Ethylenediamine HCl							
ES	570	0	0.2	0.7	0.9	1.0	0–1.9
NL-01	599	1.3	0.5	0.2	0.7	0.6	0–1.2
(e) Thiomersal							
ES	570	0	1.8	4.7	6.5	7.8	5.2–10.4
NL-01	599	0.5	0.3	0.3	0.7	0.6	0–1.3
(f) Caine mix							
ES	570	0	0.2	2.3	2.5	2.2	1.0–3.4
NL-01	599	0.5	0.8	0.2	1.0	0.9	0.2–1.6
(g) Hydrocortisone 17-butyrate							
ES	570	0	0.2	0	0.2	0.1	0–0.4
NL-01	599	2.3	0.3	0	0.3	0.3	0–0.7
(h) Carba mix							
ES	570	0.4	1.4	0.5	1.9	2.6	1.0–4.2
NL-01	599	2.2	2.7	1.0	3.7	3.3	1.9–4.6

CI, confidence interval; ES, Spain; IR, irritant reaction; NL, The Netherlands; Stand., standardized for age and sex.

screening haptens need to be relevant, and an assessment of this in one centre is shown in Table 3. The article of Bruze et al. (1) recommends inclusion when the contact allergy prevalence is 0.5–1% and above.

Allergens to add

Sodium metabisulfite 1% pet. was tested in the baseline series of three countries, with a percentage of positive reactions (Table 1) potentially justifying inclusion in the baseline series. There appears to be agreement that a 1% concentration is the most sensitive (10) and is a marker of allergy to other sulfites (11, 12). Although relevance can be hard to establish (13), the frequency of reactions is such that inclusion in the baseline series should be considered, with this preservative being widely used in cosmetic products, medicaments, industry, and food.

Table 3. Proposed changes to the baseline series with results of testing with the baseline series of one UK centre during 2016 in 1019 patients. Additional haptens in bold have a prevalence that is insufficient to warrant further inclusion. All allergens in pet.

	% Positive	95%CI	% CR	% PR/NR
Hapten to add (based on our data)				
Sodium metabisulfite 1%	2.9	1.9–4.1	1.8	1.1
2-Bromo-2-nitropropane-1,3-diol (Bronopol) 0.5%	0.39	0.11–1.0	0.29	0.10
Diazolidinyl urea 2%	0.79	0.34–1.5	0.69	0.10
Imidazolidinyl urea 2%	0.39	0.11–1.0	0.39	0
Propolis 10%	1.3	0.68–2.2	1.2	0.10
Compositae mix 5% or 6%	0.49[a,b]	0.16–1.1	0.29	0.20
Carba mix 3%	0.98	0.47–1.8	0.69	0.30
1,3-Diphenylguanidine 1%	0.1	0–0.55	0.10	0
Hapten to add (based on the literature)				
2-Hydroxyethyl methacrylate 2%	1.4	0.75–2.3	0.98	0.39
Linalool hydroperoxide 1%	4.7	3.49–6.2	4.2	0.49
Limonene hydroperoxide 0.3%	4.3	3.15–5.8	3.9	0.39
***Melaleuca alternifolia* 5%**	0.29	0.06–0.86	0.29	0
***Mentha piperita* 2%**	0.22	0.02–0.71	0.20	0
Santalum album 2%	0.59	0.22–1.3	0.49	0.1
Hapten to switch				
Caine mix III 10%	0.39	0.11–1.0	0.2	0.1
Black rubber mix 0.6%	NT	–	–	–
Hapten to delete				
Clioquinol 5%	0.1[c]	0–0.55	0.1	0
Primin 0.01%	NT	–	–	–

[a]Compositae mix tested at 2.5%.
[b]Sesquiterpene lactone mix 0.1% pet. gave 0.29% positive reactions by comparison.
[c]Quinoline mix 6% pet. tested.
CI, confidence interval; CR, current relevance; NR, not relevant; NT, not tested; PR, past relevance.

Formaldehyde releasers: diazolidinyl urea, imidazolidinyl urea and Bronopol (2-bromo-2-nitropropane-1, 3-diol) are already added to an extended baseline series in many countries (Table 1). The frequency of positive reactions would appear to justify inclusion. These formaldehyde-releasing preservatives are commonly not suspected clinically, and have been included in national baseline series in several countries (14, 15).

Fragrance(s) are currently screened within the baseline series, but there is a recognition that the current screen is inadequate. Individual groups have taken varying approaches, including testing of multiple individual fragrance allergens, namely, those 26 fragrances that currently need to be labelled according to the Cosmetics Regulation (16), testing with oxidized allergens, especially those of limonene and linalool (17), and using essential oils (18). It seems likely that testing with limonene hydroperoxide 0.3% pet. and linalool hydroperoxide 1% pet. (19) together with oils of *Melaleuca alternifolia*, *Mentha piperita* and *Santalum album* (20) (which contain allergens predominantly other than those in the baseline series plus limonene and linalool) might be a way of maximizing yield while minimizing the number of additional allergens tested. However, the irritancy of hydroperoxides is an issue at the concentrations mentioned. A recent study testing routinely with all 26 allergens that require labelling showed that, in addition to linalool and limonene hydroperoxides, *Evernia furfuracea* yielded a significant number of additional relevant reactions (21). The routine testing of the 26 substances that currently need to be labelled – with limonene and linalool in their oxidized forms – or at least of those of these haptens that have proven to be important in terms of frequency of sensitization can be viewed as a useful strategy. From a practical perspective, both previous exposure and, thus, relevance can be verified, and future avoidance can be managed, thanks to the labelling. Although we may not yet have identified an ideal combination, given the high frequency of false-negative results for fragrance allergy when only the current screening fragrance mixes are used, it seems essential to add additional fragrance allergens to an extended baseline series.

Propolis 10% pet. was tested in seven countries (Table 1), with, apart from the United Kingdom, a frequency of reactions justifying inclusion. Notwithstanding the current low prevalence of positives in the United Kingdom, in the past propolis has been included

in the British baseline series (22), when the prevalence of allergy was 1.9% among those tested. Patients who are allergic to propolis frequently co-react with colophonium and fragrances (23), and, given the current popularity of 'natural' products and its widespread use (24), it would seem that more extensive testing throughout Europe may be justified.

Compositae mix 5/6% pet. has been recognized as being a useful supplement to sesquiterpene lactone mix 0.1% pet. for detection of allergy to members of the Compositae/Asteraceae family of plants (25, 26). Although some have found that the additional yield over and above sesquiterpene lactone mix alone is insufficient to warrant additional testing in a baseline series in Sweden (27), the notion remains that sesquiterpene lactone mix alone is an inadequate screen (28, 29), warranting further study. The commercial allergen tested at 5% has also been shown to be sensitizing (30), with equal numbers of patients being sensitized and additional allergic patients detected. This is not a property desirable for any screening allergen. In the United Kingdom, a lower concentration of Compositae mix II, that is, 2.5% pet. (Chemotechnique Diagnostics, Vellinge, Sweden), has been included in the baseline series for many years, without evidence of active sensitization, but continued sensitivity in the detection of Compositae allergy (Table 3).

1,3-Diphenylguanidine 1% pet. is a rubber accelerator contained within the 'carba mix', although it is not a dithiocarbamate. Recent studies of rubber allergy from the ESSCA (31) and EPIDERM (32) suggest that carba mix is causing more frequent allergic reactions, although concerns have been raised about the irritancy of the patch test preparation. Many manufacturers of gloves have switched from thiuram to carbamates as accelerators, raising the possibility that carbamates, as a consequence of increased exposure, may be sensitizing more frequently. However, thiuram mix is thought to be an adequate screen for carbamate allergy (33), as both exist as a redox pair in equilibrium *in vivo*, with thiuram mix being the better marker of contact allergy (34). Consequently, it is thought that 1,3-diphenylguanidine may be responsible for the increasing prevalence of reactions to the carba mix. Although there is no definitive answer, consideration should be given to testing more widely with zinc diethyldithiocarbamate 1% pet. and 1,3-diphenylguanidine to avoid false-negative reactions. However, given the low yield from testing with 1,3-diphenylguanidine alone (Table 3), it may be better to restrict this to a rubber series (35) and patients with hand dermatitis.

2-Hydroxyethyl methacrylate (2-HEMA) 2% pet. has previously been used as a marker of contact allergy to methacrylates (36). Traditionally, exposure was occupational, but the recent fashion for acrylate-containing nail products is resulting in increases in the numbers of cases of non-occupational hand and facial dermatitis (37, 38). Although data on systematic testing in the current environment do not exist, it seems probable that consideration needs to be given to evaluating more extensive testing with acrylates to avoid missing what is becoming an increasingly common contact allergen in a domestic setting. In the previous study from 2008 (14), 63% of sensitized patients would have been missed if acrylates had not been tested routinely. Sensitization is also a concern when acrylates are tested (39). The high frequency of sensitization reported was attributable to various acrylates, that is, ethyl acrylate, 2-hydroxy ethyl acrylate, etc., and not to methacrylates such as 2-HEMA. After testing of > 1000 patients with 2-HEMA in a baseline series, no cases of active sensitization became apparent (Table 3), even though patients are encouraged to return if they develop late reactions. As users of acrylate nails are predominantly female, another way to reduce exposure and sensitization risk would be to create a sex-specific baseline series.

Allergens to switch

Caine mix III 10% pet. This mix, containing benzocaine, cinchocaine (dibucaine), and tetracaine, the latter two as hydrochlorides, has long been used instead of benzocaine 5% pet. in the baseline series in the United Kingdom (40, 41). Data from the ESSCA, as they do not provide a direct comparison, are unable to confirm that more widespread use of caine mix III across Europe would be beneficial, but do suggest that instituting a more widespread comparison would be of value. In general, those centres of the ESSCA testing caine mix III had a higher yield of positive results than obtained with benzocaine 5% pet. (8) during the same time period. Lidocaine (lignocaine) is an amide local anaesthetic that does not cross-react. However, there are increasing reports of contact allergy; in one study, when lidocaine was included in a medicament series, there were more cases of contact allergy to lidocaine than to other topical anaesthetic agents (42). This suggests that the usefulness of including lidocaine as a screening agent should be evaluated.

Black rubber mix 0.6% pet. may prove a better screen for rubber antioxidants than *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD) 0.1% pet. (31) alone. A prospective comparison may help to provide evidence of the superiority of one above the other, ideally based on thorough relevance assessment and/or breakdown testing of mix constituents.

Allergens to omit

Testing with the baseline series in departments of the ESSCA during 2013–2014 suggests that two allergens in particular should be considered for removal from the EBS.

Primin 0.01% pet., with an age- and sex-standardized prevalence of allergy of 0.2% (95%CI: 0.2–0.3%), no longer appears to warrant inclusion. The development of hypoallergenic varieties of *Primula obconica* and the subsequent reduction in the frequency of contact allergy to the plant is well documented (43). However, patch testing may still be relevant in subgroups of the population (e.g. retirees and household workers in Italy) (44), and addition to a plant series may be a better option for more selected testing.

Clioquinol 5% pet., with an age- and sex-standardized prevalence of allergy of 0.3% (95%CI: 0.2–0.4%), also appears to yield insufficient allergic reactions to warrant continued inclusion. This probably reflects changing prescribing habits and an aversion to the yellow staining of this topical antiseptic, exposure to which may quite easily be identified by proper history-taking, enabling aimed testing as indicated.

Conclusion

It is hoped that the above discussion has highlighted some areas for further investigation. We propose that a (temporary) (45) supplement to the baseline series (Table 3) might prove to be a useful way of evaluating the need to test more widely, and prove to be a practical way of being more responsive to changes in environmental allergen exposure while further information is gathered.

It is inevitable that there will be regional and national differences requiring additions to the above, depending on local exposures, that national societies will continue to recommend: for instance, ethylenediamine dihydrochloride remaining in the Spanish baseline series (46).

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